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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte THOMAS CURRAN and LAKHU KESHVARA

Appeal 2010-005812
Application 10/078,927
Technology Center 1600

Before DEMETRA J. MILLS, FRANCISCO C. PRATS, and MELANIE L. McCOLLUM, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

STATEMENT OF CASE

The following claims are representative:

36. A method for detecting cyclin dependent kinase 5 (Cdk5) serine kinase activity in a biological sample, which method comprises determining whether the carboxy terminal domain of Disable 1 protein (Dab1) in said sample is phosphorylated on a serine within a candidate sequence, wherein phosphorylation of Dab1 on said serine indicates the presence of active Cdk5 in said sample.

38. A method for detecting cyclin dependent kinase 5 (Cdk5) serine kinase activity in a biological sample, which method comprises immunoprecipitation of Dab1 from said biological sample; contacting the immunoprecipitated Dab1 with a phosphoantibody generated using SEQ ID NO:3 as an antigen; detecting binding of the phosphoantibody to a serine within a candidate sequence in the carboxy terminal domain of said Dab1, wherein binding of the phosphoantibody to said serine of said Dab1 in such biological sample indicates the presence of Cdk5 serine kinase activity in said sample.

Cited References

Curran et al. US 6,323,177 B1 Nov. 27, 2001

Carr et al., *Selective Detection and sequencing of Phosphopeptides at the Femtomole Level by Mass Spectrometry*, 239 ANALYTICAL BIOCHEMISTRY 180-192 (1996).

GenBank GI:1771281, *M. musculus mRNA for mDab555 protein*, February 1997.

GenBank GI:3288851, *Homo sapiens disbled-1 (DAB1) mRNA*, November 1998.

Michalewski et al., *Immunoblotting with Antiphosphoamino Acid Antibodies: Importance of the Blocking Solution*, 276 ANALYTICAL BIOCHEMISTRY 254-257 (1999).

Niethammer et al., *NUDEL Is a Novel Cdk5 Substrate that Associates with LIS1 and Cytoplasmic Dynein*, 28 NEURON 697-711 (2000).

Keshvara et al., *Identification of Reelin-induced Sites of Tyrosyl Phosphorylation on Disabled 1*, 276 J. BIO. CHEM. 16008-16014 (2001).

Fu et al., *Cdk5 is involved in neuregulin-induced AChR expression at the neuromuscular junction*, 4 NATURE NEUROSCIENCE 374-381 (2001).

Zhen et al., *Prenatal Exposure to Cocaine Disrupts D_{1A} Dopamine Receptor Function Via Selective Inhibition of Protein Phosphatase 1 Pathway in Rabbit Frontal Cortex*, 21 J. NEUROSCIENCE 9160-9167 (2001).

Grounds of Rejection

1. Claims 4-8 and 36-37 are rejected under 35 U.S.C. § 103(a) for obviousness over Curran in view of Keshvara, Niethammer, Carr, GenBank and GenBank.

2. Claims 10-11, 13-15 and 38 are rejected under 35 U.S.C. § 103(a) for obviousness over Curran in view of Keshvara, Niethammer, Carr, GenBank and GenBank, Howard, Fu and Michalewski.

FINDINGS OF FACT

The findings of fact relevant to all rejections are set forth below.

1. The reference of Curran teaches "In vitro cdk5 can also phosphorylate Dabl on serine residues" (col. 4, ll. 46-47) and "In particular, identification of the site of Dabl phosphorylation may permit its use as a potential target for agonists and antagonists. Cdk5 phosphorylates Dabl in vitro. We can screen for inhibitors and agonists of this activity in connection with Reelin binding to VLDLR, and map the phosphorylation sites. Cdk5 has been

implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in AD [Alzheimer's Disease]. Thus, this area of exploration has significant relevance" (col. 23, l. 63 to col. 24, l. 4).

2. The Examiner finds that

> The differences between Curran and the claimed methods are: Curran does not teach those residues of Dab1 that are phosphorylated by Cdk5; Curran does not teach Dab1 is phosphorylated in biological sample *e.g.,* brain and blood, from a mouse or human; and Curran does not teach methods of measuring Cdk5 activity by determining whether or not Dab1 is phosphorylated at these residues.

(Ans. 5.)

3. According to the Examiner

> The references of Niethammer, Keshvara, and Carr are cited as showing various methods for analyses of a phosphoprotein. Regarding the limitations of claims 4-5, 7-8, and 36-37, the reference of Niethammer teaches a method for determining the sites of phosphorylation of a substrate polypeptide of Cdk5. For example, the method involves immunoprecipitation of the substrate polypeptide from mouse brain extracts with or without catalytically active Cdk5 activity and determining whether or not the substrate protein has altered electrophoretic mobility (p. 704, Figures 7A, 7D, and 7E and p. 709, column 1); teaches identifying those amino acids that are potentially phosphorylated by Cdk5 kinase in the primary sequence of the polypeptide, which have serine-proline (p. 703, column 2, bottom and p. 698, Figure IA); individually and combinatorially mutating the potential Cdk5-phosphorylated serine residue to an alanine; comparing the electrophoretic mobility shift in migration of immunoprecipitated wild-type and mutant proteins in the presence and absence of catalytically active Cdk5 in COS7 cells; and identifying those residues that are phosphorylated by Cdk5 by comparing the Cdk5 phosphorylation of the wild-type, individual mutants, and

> combinatorial mutants (p. 704, Figure 7F and p. 708, column 1 to p. 709, column 2).

(Ans. 5-6.)

4. The Examiner finds

> [r]egarding the limitations of claims 6-7 and 36-37, the reference of Keshvara teaches a method of identifying sites of tyrosine phosphorylation of Dab1 by Src, using a method similar to that of Niethammer, wherein the tyrosine residues phosphorylated by Src are identified by mutating each potential Src-phosphorylated tyrosine to phenylalanine and analyzed by autoradiography and tryptic phosphopeptide analysis (p. 16009, Figure 1A-B and column 1 under *Kinase Reactions* and *Phosphopeptide Mapping;* p. 16010, Figure 2A-B). Keshvara teaches an expression vector encoding Dab1 for use in expressing Dab1 in a eukaryotic cell (p. 16009, under *Cell Culture* and *Immunoprecipitations*).

(*Id.* at 6-7.)

5. The Examiner concludes that

> at the time of the invention it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Curran, Niethammer, Keshvara, and GenBank Accession Numbers 1771281 and 3288851 to immunoprecipitate Dab1 from a mouse brain extract with and without catalytically active Cdk5 (as taught by Niethammer) and analyze its electrophoretic mobility and to determine whether or not serine at positions 260, 400, 481, 491, and 515 are phosphorylated in accordance with the methodology of Niethammer and Keshvara. One would have been motivated to do this because of the teachings of Curran that Cdk5 phosphorylates Dab1; the sites of Cdk5 phosphorylation of Dab1 can be identified; and may have "significant relevance" to screen for agonists and antagonists because Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in AD.

(Ans. 7.)

6. The Examiner further concludes that

> [o]ne would have had a reasonable expectation of success to immunoprecipitate Dab1 from a mouse brain extract with and without catalytically active Cdk5 (as taught by Niethammer) and analyze its electrophoretic mobility and to determine whether or not serine at positions 260, 400, 481, 491, and 515 are phosphorylated in accordance with the methodology of Niethammer and Keshvara because of the results of Curran, Niethammer, Keshvara, and GenBank Accession Numbers 1771281 and 3288851.

(*Id.* at 7-8.)

7.

> Alternatively, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Curran, Keshvara, and Carr to immunoprecipitate Dab1 from mouse brain extract with catalytically active Cdk5 to determine its potential site(s) of phosphorylation according to the phosphopeptide analysis method of Carr. By doing this, one of ordinary skill in the art would have practiced the active method step(s) as recited in the claims. One would have been motivated to do this because of the teachings of Curran that Cdk5 phosphorylates Dab1; the sites of Cdk5 phosphorylation of Dab1 can be identified; and may have "significant relevance" to screen for agonists and antagonists because Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in AD.

(*Id.* at 8.)

8. The Examiner concludes that

> [o]ne of ordinary skill in the art would have had a reasonable expectation at the time of the invention to combine the teachings of Curran, Keshvara, and Carr to immunoprecipitate

> Dab1 from mouse brain extract with catalytically active Cdk5 to determine its potential site(s) of phosphorylation according to the phosphopeptide analysis method of Carr.

(Ans. 8.)

Discussion

ISSUE

Appellants argue that none of the prior art cited by the Examiner teaches or suggests that the candidate sequence within the carboxy terminal domain of Dab1 is selectively serine phosphorylated by Cdk5, as claimed. (App. Br. 4). Appellants argue that there is no motivation to combine the cited references (*id.* at 5) and that there is no suggestion in the cited references that Cdk5 selectively phosphorylates Dab1 in a biological (in vivo) sample, nor do they teach which serines might be selectively phorphorylated by Cdk5. (*Id.* at 6.)

The issue is: Does the prior art disclose or suggest to one of ordinary skill in the art the detection of Cdk5 activity in a sample by phosphorylation of Dab1? Does the prior art disclose or suggest which serines on Dab1 are phosphorylated by Cdk5?

PRINCIPLES OF LAW

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). In order to determine whether a prima facie

case of obviousness has been established, we consider the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966): (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

ANALYSIS

Upon review of the evidence of record, we agree that the Examiner has presented a prima facie case that the method of claim 36 would have been obvious. The Examiner provides evidence, Curran, that Dab1 is phosphorylated by Cdk5 at serine residues, thus revealing the presence of Cdk5 upon detection of phosphorylation of Dab1 in a sample. This process is suggested to be an important pathway, as Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in the brain in Alzheimer's disease. (Curran, col. 23 and 24.) The GenBank references provide evidence of the location of serine residues in Dab1. Niethammer evidences that there is a well known method to determine phosphorylation of a substrate by Cdk5 in brain lysates by mutation of serine residues. (Niethammer, p. 704.) Thus, one of ordinary skill in the art with this knowledge would have been led to determine which residues of Dab1 are phosphorylated by Cdk5 in brain tissue because Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in the brain in Alzheimer's disease. One of ordinary

skill in the art would have been provided with the means to determine phosphorylation by the well known methods disclosed in Niethammer. One of ordinary skill in the art determining the phosphorylation of Dab1 by Cdk5 inherently detects cyclin dependent kinase 5 (Cdk5).

Appellants argue that none of the prior art cited by the Examiner teaches or suggests that the candidate sequence within the carboxy terminal domain of Dab1 is selectively serine phosphorylated by Cdk5, as claimed. (App. Br. 4.) Appellants argue that the prior art does not teach which serines might be selectively phorphorylated by Cdk5. (*Id.* at 6.) However, the cited prior art provides the location of serine residues in Dab1. One of ordinary skill in the art determining which serines are phosphorylated in Dab1 by the well known methods of Niethammer would determine phosphorylation of the serine at the carboxy terminal domain of Dab1 as well as other phosphorylated serine residues. (Ans. 12-13.)

Even though the Examiner stated that he would read the preamble and wherein clause in claim 36 as intended use of language having no bearing on patentability (*id.* at 13), the motivating disclosure in Curran states that Cdk5 phosphorylates Dab1 at serine residues and this important pathway has been implicated in the brain disorder, Alzheimer's disease. Thus the motivating disclosure cited by the Examiner actually provides a reason to detect Cdk5 phosphorylation of Dab1 in a brain sample, consistent with the preamble language, as claimed.

Appellants argue that there is no suggestion in the cited references that Cdk5 selectively phosphorylates Dab1 in a biological (in vivo) sample. For the reasons given herein, Curran provides a reason to detect Cdk5

phosphorylation of Dab1 in a brain sample, in vivo, through its implication of its association with an important pathway found in Alzheimer's disease.

Patentability determinations are based on a preponderance of the evidence. "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

Upon review of the evidence of record, Appellants have failed to rebut the Examiner's prima facie case of obviousness, and a preponderance of the evidence supports the obviousness rejection. The obviousness rejection is affirmed.

2. Claims 10-11, 13-15 and 38 are rejected under 35 U.S.C. § 103(a) for obviousness over Curran in view of Keshvara, Niethammer, Carr, GenBank and GenBank, Howard, Fu and Michalewski.

Appellants argue that this rejection suffers from the same deficiencies as the first rejection. (App. Br. 7.) For the reasons given for rejection 1, the obviousness rejection is affirmed.

CONCLUSION OF LAW

The cited references support the Examiner's obviousness rejections.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

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